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PERSONAL AUTHOR(S)
Donald B. Boyd, David W. Smith, James J.P. Stewart, and Erich Wimmer

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Numerical Sensitivity of Trajectories across Conformational Energy Hypersurfaces from Geometry Optimized Molecular Orbital Calculations: AM1, MNDO, and MINDO/3

Donald B. Boyd* and David W. Smith

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

James J. P. Stewart

The Frank J. Seiler Research Laboratory, United States Air Force Academy, Colorado Springs, Colorado 80840

Erich Wimmer

Cray Research, Inc., 1333 Northland Drive, Mendota Heights, Minnesota 55120

The monocyclic β-lactam [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid was studied by the semiempirical molecular orbital methods AM1, MNDO, and MINDO/3. Using the reaction coordinate option in the program MOPAC on VAX and Cray X-MP computers, the potential energy curve was calculated for rotation of the C2-N1-S-C torsional angle in the conformationally flexible side chain while optimizing all other geometrical variables in the molecule. The trajectory taken during geometry optimization was found to be sensitive to the computer, the program version, the convergence criteria, and the degree of code optimization used in the calculation. In order to reduce the likelihood of spurious results, conformational or reaction energy hypersurfaces need to be calculated with the more precise SCF convergence and minimization criteria available in programs for MINDO/3, MNDO, and AM1 calculations. The nitrogen in the model β-lactam antibiotic is predicted to invert periodically as the dihedral angle to the exocyclic N-substituent sweeps through 360°.

INTRODUCTION

One of the most widely used computational chemistry[1-3] programs currently available is MOPAC.[4,5] MOPAC can run three popular semiempirical, all-valence-electron molecular orbital methods: MINDO/3,[6] MNDO,[7] and AM1.[8] These methods are capable of giving fairly reliable equilibrium bond lengths, bond angles, and conformations, molecular energies (heats of formation), ionization potentials, dipole moments, vibrational frequencies and intensities, transition state geometries, and thermodynamic properties of organic, pharmacological, biochemical, and some inorganic molecular structures. The methods have been reviewed elsewhere.[8-10] MINDO/3, the oldest of these methods, has been used in over 260 papers.[11]

The importance of MOPAC and kindred programs (MINDO/3,[12-14] MNDO,[15,16] and AMPAC[17]) to past and present computational chemistry and computer-assisted molecular design research is exemplified by the fact that a sizable proportion of all papers reporting molecular orbital results in the chemical literature has been based on these programs. This situation will continue. MOPAC and AMPAC were the programs most requested from the Quantum Chemistry Program Exchange (Indiana University, Bloomington, IN) in a recent 16-month period. The total number of copies of MOPAC and AMPAC distributed (230) far exceeded that for any other computational chemistry program including GAUSSIAN80-UCSF[18] (56) and MM2[19,20] (42). The MOPAC and AMPAC programs are sufficiently comprehensive and versatile that they are used both stand alone and integrated with computer-assisted molecular design (CAMD) software systems.[21-23]

MOPAC is written[4,5] in transportable FORTRAN-77 so that it can be run fairly

*To whom correspondence should be addressed.

easily on a number of computer brands, including the Digital Equipment Corporation VAX computer series, which is now almost universally used in computer-assisted molecular design studies.[1] However, as larger and larger research problems are attached with MOPAC, it is inevitable that supercomputers, such as a Cray, will be required. Already many hardware vendors, both major and minor, have adapted or are adapting MOPAC to their machines.

We wish to report our experience with MOPAC running on a Cray X-MP/416. We also report central processing unit (CPU) times to compare the efficiency of running MOPAC on Cray and VAX machines.

An unexpectedly large variability in the energy hypersurface was found for the test case on *both* the VAX and the Cray. This discovery suggests a vulnerability of conformational predictions from this program and related programs, all of which are based on the Davidon–Fletcher–Powell geometry optimization procedure.[6,24–27] The routine for doing this procedure, FLEPO, is used in a number of quantum mechanical programs. Despite the widespread use of MOPAC and AMPAC and their progenitors, the minimization technology used in the programs has apparently been taken at face value by most users.

Our test case was a pragmatic one involving the conformation of [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid. This structure is a model of the sulfur analogue of [[3(S)-(acylamino)-2-oxo-1-azetidinyl]oxy]acetic acids (oxamazins), a new class of monocyclic β-lactam antibiotic.[28–30] The reaction coordinate was the C2-N1-S-C dihedral angle to the S-CH₂-COOH side chain. As recommended by Dewar,[10] all calculations were carried out with full geometry optimization, except, of course, for the dihedral angle that defines the reaction coordinate. Thus a multidimensional potential energy surface (hypersurface) is being computed. In order to save computer time in generating trial density matrices, MOPAC and related programs use the output geometry from each point in the reaction coordinate path as input for the next point. Thus, the course of a reaction coordinate run can be influenced by all prior geometries. This test case is obviously rigorous, as well as being prototypical of many uses of MOPAC in computer-assisted drug design studies.[21,29]
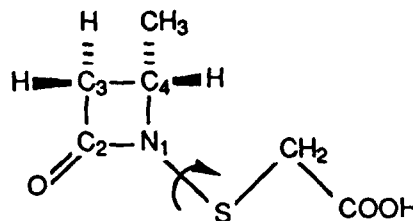
METHODOLOGY

The AM1 method, which is the most recent molecular orbital (MO) method from the Dewar group[8] and the only method in MOPAC capable of satisfactorily treating hydrogen-bonding interactions and structures with rotational freedom about single bonds between sp^2-hybridized atoms, was chosen for most of the calculations. Optimized AM1 parameters for sulfur have not yet been published. Version 3.1 of MOPAC does AM1 calculations on sulfur-containing structures using sulfur parameter values that are identical or similar to those reported for the MNDO method.[31] While these substitute values may not be ideal for AM1, the MNDO-like sulfur parameters give reasonably good results in AM1[29,32] and probably will not be drastically different than the ultimate AM1 values. MNDO and MINDO/3 are applied here in addition to AM1. Regarding MINDO/3, it has been pointed out[33] that the sulfur MINDO/3 parameters widely used in MOPAC and related programs are not those used in the original study.[6] Discrepancies in the MINDO/3 and MNDO parameterization have persisted, and the parameter values in the programs seem to have become the *de facto* standard through use. We emphasize that parameterization is not at issue in this investigation. The minimization procedure is. The vagaries of the minimization procedure could show up with any parameterization.

The series of conformers discussed here was generated in a reaction coordinate run where the dihedral angle controlling the side chain conformation is driven through 360° in 30° increments. All the calculations used identical geometrical data as input. All 54 geometrical variables, which were specified in internal coordinates, had been energy optimized in a separate earlier AM1 calculation using the default options in MOPAC Version 3.0 running on a VAX 8600 computer.[29] The optimized C2-N1-S-C dihedral angle was 118.5°. The reaction coordinate runs all started by reoptimizing the starting geometry with the

C2-N1-S-C dihedral angle at 118.5° (conformer #1). The second conformer has the angle set at 140°, the third at 170°, etc., until at conformer #14 the dihedral angle is again at 140°.

The floating point operations were done in double precision (64-bit words) on the VAX 8600 and 8800 computers. The Cray X-MP/416 uses a 64-bit single precision word, but has a shorter mantissa (48 bits) than that of a double precision word on VAX machines (55 bits). Hence the number of significant figures in intermediate-sized numbers is greater on a VAX, although the Cray handles larger and smaller exponents.

MOPAC Versions 3.0 and 3.1 are the standard ones available from the Quantum Chemistry Program Exchange.[4,5] Version 3.11 is a new version under development by Stewart[34] for the Cray which corrects some numerical instabilities in matrix diagonalization which showed up on that machine in the quantities $(1-q^2)^{1/2}$ when q approaches 1. This arithmetic, which has been recoded in MOPAC 3.11, caused numerical errors of the same order of magnitude as the convergence criteria. The new code also allows better vectorization, notably in the generation of the Fock matrix.

The complex convergence and optimization criteria built into MOPAC (and AMPAC) are described in the program manual and documentation[4,5] and need not be repeated here. In part the default self-consistent field convergence criterion is a drop in electronic energy of less than 0.00001 kcal/mol on two successive iterations. For geometry optimization the default Davidon–Fletcher–Powell criteria can be a projected change in geometry of less than 0.0001 Å (or radians) ("test on X"), a projected decrease in energy of less than 0.001 kcal/mol ("Herbert's test"), a gradient norm of less than 1.0 kcal mol^{-1} Å^{-1} (or kcal mol^{-1} rad^{-1}) ("test on gradient"), or a change in calculated heats of formation on two successive iterations of less than 0.002 kcal/mol ("heat of formation test"). By using the keyword PRECISE in the input data to the program, the SCF criterion is made 100 times smaller, and the four geometric criteria are made 100, 100, 500, and 50 times smaller, respectively. Depending on the type of calculation being done, the criteria are adjusted automatically by the program to enhance performance.

For the test case studied here, all calculations reached SCF convergence. The number of conformers which satisfied Herbert's test ranged from 6 to 14 per run. In the remaining conformers, the gradient test was not passed, but further work was not justified because of the shallowness of the energy gradient.

RESULTS

The potential energy curves in Figure 1 are labeled according to the machine on which they were run, the version of MOPAC used, and whether the calculation was done with the convergence and optimization criteria tightened. Although all the curves start out similar and the height of the first barrier of the twofold potential varies less than 0.2 kcal/mol, some differentiation is seen at the first trough (conformer #6). The height of the second barrier shows greater variability of 0.3 kcal/mol. The energies of the last three conformers (#12, #13, and #14) are highly variable, and, in fact, the shapes of the curves are obviously different qualitatively.

The startling variability in the potential energy curves in Figure 1 is due to the calculations following different minimum energy pathways through the multidimensional space of the geometrical parameters. Very small differences in the numerical accuracy of the computations is causing the geometry optimization to veer down diverging paths when the potential energy surface offers several channels of very nearly equal energy. *The effect is seen on both the VAX and Cray computers.*

The only two curves of Figure 1 that are essentially identical, as one would hope that hey all would be, are for the calculations done with PRECISE. Although similar, the heats of formation for these two curves agree only to the first or second decimal place. When the calculation is done with PRECISE turned on, conformers #2 and #14 (both of which have dihedral angle C2-N1-S-C = 140°) are more nearly identical in energy. Also with PRECISE the potential energy curves correspond more closely to twofold periodicity.

Further tests were run on the Cray X-MP to explore the effects of using a newly available FORTRAN compiler, running the calculation with single-precision (64-bit) or double-precision (128-bit) words, and turning off the
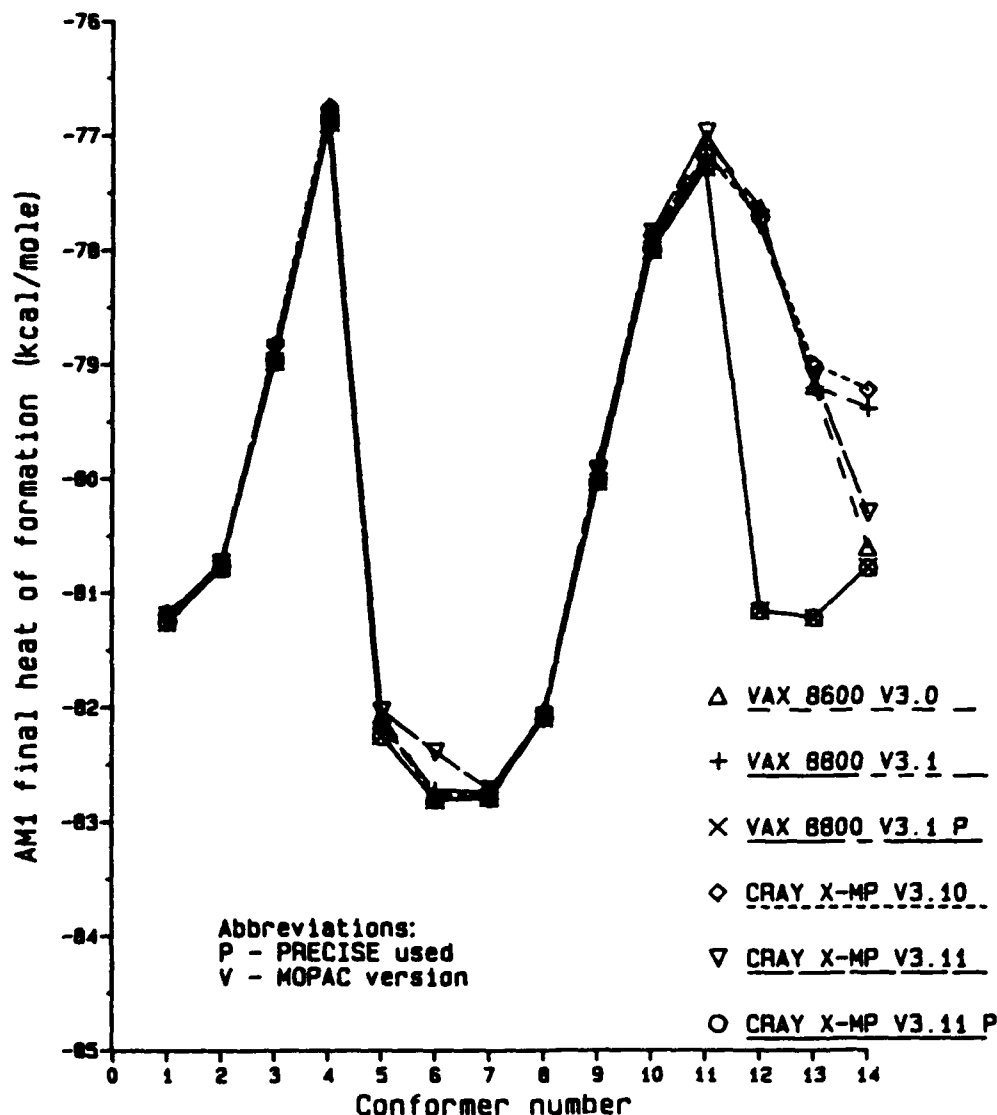
Figure 1. AM1 potential energy curves for [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid as predicted by MOPAC on VAX and Cray computers. Free geometry optimization was done on each conformer starting with an optimized geometry. Each curve is labeled according to the machine and MOPAC program version (V) used. Curves marked with P were run with the PRECISE option turned on in MOPAC.

automatic vectorization of the code. The different Cray compilers achieve different levels of automatic optimization of the operations, which implies different orders of operations. Turning vectorization on or off also implies changing the order of some operations. The Cray FORTRAN compilers allow aspects of the executable module to be invoked without having to change the MOPAC source code. As seen in Figure 2, these tests underscore the sensitivity of the MOPAC results when the calculations are done *without* PRECISE.

The potential energy profiles predicted by MOPAC using the MNDO and MINDO/3 molecular orbital methods are shown in Figures 3 and 4. The older methods also show a sensi-

tivity to the convergence and optimization criteria, although different than AM1s. The MINDO/3 curves start out on a high-energy hypersurface, but after a few conformers, the minimizer finds a lower-energy one. Subsequent conformers transverse the latter surface, which has 3–4 kcal/mol barriers to rotation about the N—S bond. The higher energy surface has a gauche N1-S-C-C conformation, while the lower one has a trans conformation (see Table IV).

The "ultimate" test was done by running the data with PRECISE in MOPAC 3.11 in double precision on the Cray X-MP. The 128-bit words correspond to 29 significant decimal places compared to 14 for 64-bit
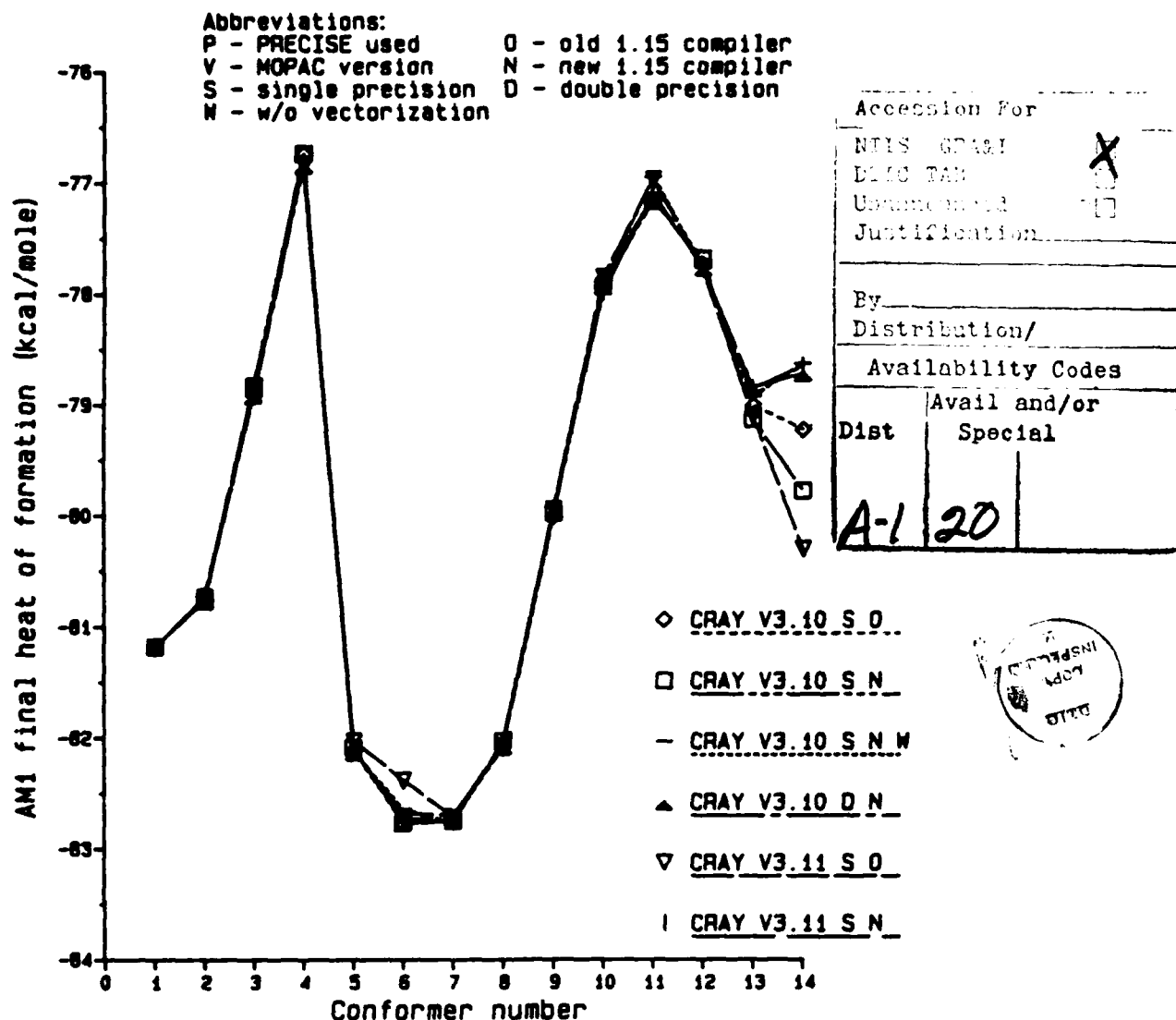
Abbreviations:
P - PRECISE used   O - old 1.15 compiler
V - MOPAC version   N - new 1.15 compiler
S - single precision D - double precision
W - w/o vectorization

◇ CRAY_V3.10_S_O

□ CRAY_V3.10_S_N

— CRAY_V3.10_S_N_W

▲ CRAY_V3.10_D_N

▽ CRAY_V3.11_S_O

I CRAY_V3.11_S_N

Figure 2. AM1 potential energy curves for [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid as predicted by MOPAC on the Cray X-MP/416. Each curve is labeled according to the MOPAC program version (V) used, whether the calculation was done with single (S) or double (D) precision, and whether FORTRAN compilation was done with the old (O) or new (N) Releases 1.15 of the Cray CFT compiler (see footnotes to Table I). The curve marked W was run without automatic vectorization.

words normally used on the Cray. The AM1 method was used. The curves in Figure 5 show that the calculated hypersurface has stabilized for this molecule, and no further variability is revealed at the highest level of numerical accuracy.

The computer time requirements are given in Table I. MOPAC ran the AM1 calculations 13–15 times faster on one processor of the Cray X-MP/416 than on one processor of a VAX 8800. Vectorization has no effect on the potential energy curve, and only gives a two-fold improvement in speed. Turning PRECISE on causes the calculations to run 2–4 times longer. The PRECISE, double-precision calculation on the Cray consumed a huge amount

of CPU time, taking almost as long as the PRECISE run on the VAX 8800.

DISCUSSION OF MOLECULAR STRUCTURE

The seeming capriciousness of the results due to small round-off errors being magnified to chemical significance by the minimization procedure is seen in the two sets of N1-S-C-C dihedral angles in Table II which diverge dramatically at conformer #11. The differences in the conformations can be appreciated from the ORTEP[35] ball-and-stick molecular graphics in Figure 6.

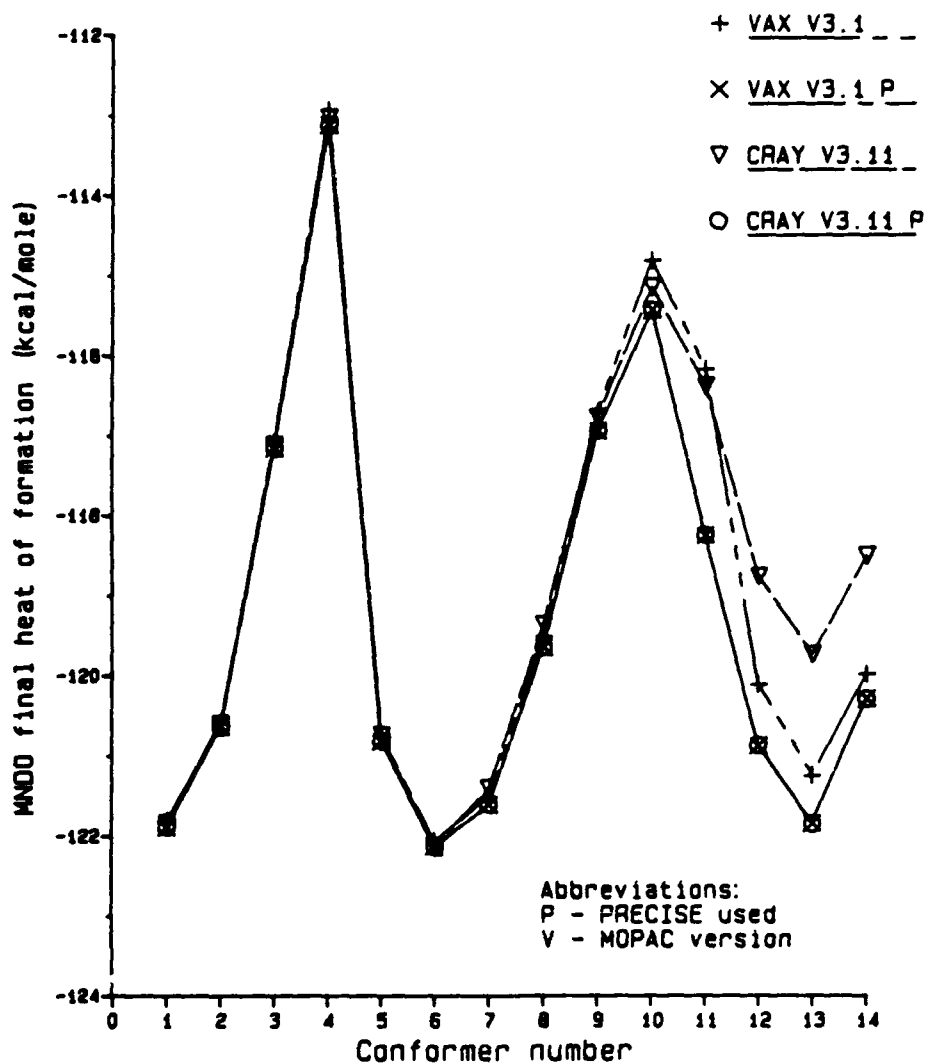The pyramidal character of the β-lactam nitrogen is most clearly measured by the dis-

Figure 3. MNDO potential energy curves for [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid as predicted by MOPAC 3.1 on VAX 8800 and Cray X-MP/416 computers. The curves marked with P were run with the PRECISE option turned on.

tance h that this atom is out of the plane of its three substituents. The twofold variation in distance h as a function of the conformation of the side chain found with the PRECISE AM1 calculations (Table II) is an interesting property not previously reported. According to the minimizer, the molecule reaches a lower energy by inverting the β-lactam nitrogen when the C2-N1-S-C dihedral angle is near $-120°$ and $60°$. As the side chain is twisted, inversion occurs upon approaching the minimum after the first barrier (Fig. 1). Then the molecule inverts back to its original configuration when beginning to mount the next potential energy peak. Inversion again occurs when approaching the second minimum, but immediately flips back at the next conformer. As seen in Tables III and IV, the MNDO and

MINDO/3 methods when used with the PRECISE criteria corroborate the inversions predicted by AM1.

In contrast, in oxamazin,[29] the oxygen analogue of thiamazin, the β-lactam nitrogen is predicted by the AM1 method (with PRECISE) to *retain* its configuration as the side-chain conformation changes. The oxygen analogue is predicted to have a more pyramidal β-lactam nitrogen,[29] so there is less proclivity to invert.

It is also of interest from a chemical point of view that AM1 and MNDO predict the β-lactam nitrogen of thiamazin to be much more pyramidal than does MINDO/3 (Tables II–IV). AM1 predicts the highest h values (0.3–0.5 Å), while MNDO gives extremes of 0.3–0.4 Å. MINDO/3's prediction of

Table I. Central processor unit time required for tests of MOPAC.

Machine	MOPAC version	Cray compiler	PRECISE	Time (s)	Relative time
		AM1			
VAX 8600	3.0	—	—	10888	28
VAX 8800	3.1	—	—	5919	15
VAX 8800	3.1	—	on	20603	53
Cray X-MP/416[a]	3.10	old[b]	—	393	1
Cray X-MP/416	3.11	old[b]	—	460	1.2
Cray X-MP/416	3.11	old[b]	on	1581	4
Cray X-MP/416	3.10	new[c]	—	452	1.1
Cray X-MP/416	3.10	new[d]	—	831	2
Cray X-MP/416	3.10	new[e]	—	7324	19
Cray X-MP/416	3.11	new[c]	—	389	1
Cray X-MP/416	3.11	new[f]	on	1456	4
Cray X-MP/416	3.11	new[g]	on	17950	46
		MNDO			
VAX 8800	3.1	—	—	6274	16
VAX 8800	3.1	—	on	16793	43
Cray X-MP/416	3.11	new[c]	—	363	1
Cray X-MP/416	3.11	new[c]	on	977	2.5
		MINDO/3			
VAX 8800	3.1	—	—	3430	9
VAX 8800	3.1	—	on	7595	20
Cray X-MP/416	3.11	new[c]	—	157	0.4
Cray X-MP/416	3.11	new[c]	on	359	1

[a]All calculations on the Cray were done on one processor of Serial Number 218, Mendota Heights.
[b]The executable module was created by the Cray compiler (December 1986–January 1987) with default options of single precision and automatic vectorization of the code.
[c]The executable module was created by the Cray compiler CFT 1.15 BF1 (February 1987) under COS 1.16 with default options of single precision and automatic vectorization of the code.
[d]Differs from the default Cray executable by having vectorization turned off during compilation and execution.
[e]Differs from the default Cray executable by having double-precision length (128-bit) words for all operations.
[f]CFT 1.15 BF2 (March 1987) compiler under COS 1.16 using Cray libraries for RSP (diagonalization) routines.
[g]CFT 1.15 BF2 (March 1987) compiler under COS 1.16 using MOPAC's internal RSP routines and with double-precision length (128-bit) words for all operations.

Table II. AM1 optimized geometrical data for C2-N1-S-C conformers of [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid obtained from MOPAC 3.1 on a VAX 8800 without and with PRECISE[a]

Conformer	C2-N1-S-C (°)	N1-S-C-C (°)		h (Å)	
		without	with	without	with
1	118.5	−63	−64	0.28	0.27
2	140	−63	−64	0.37	0.38
3	170	−55	−53	0.44	0.45
4	−160	−71	−73	0.48	0.47
5	−130	−77	−74	−0.29	−0.31
6	−100	−76	−73	−0.10	−0.09
7	−70	−76	−75	0.14	0.13
8	−40	−77	−78	0.30	0.30
9	−10	−80	−82	0.35	0.39
10	20	−94	−94	0.43	0.42
11	50	−108	−117	0.46	0.44
12	80	−110	−52	0.42	−0.16
13	110	−109	−53	0.39	0.07
14	140	−109	−66	0.41	0.38

[a]A positive torsional angle for A-B-C-D is measured clockwise from the A-B-C plane to the B-C-D plane looking from B to C. A 0° angle corresponds to cis. h is the distance the β-lactam nitrogen is out of the plane of its three substituents. A negative value of h indicates sulfur is on the same side of the amide plane as the 4α-methyl carbon.
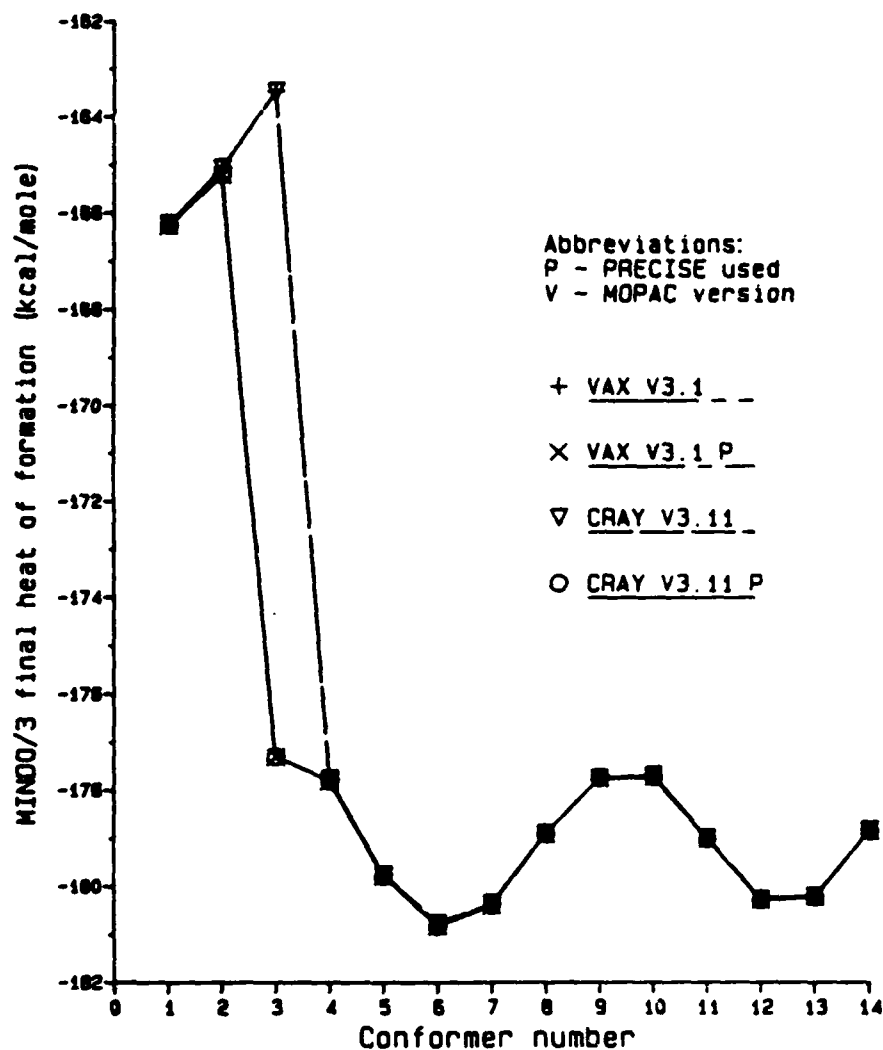
Figure 4. MINDO/3 potential energy curves for [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid as predicted by MOPAC 3.1 on VAX 8800 and Cray X-MP/416 computers. The curves marked with P were run with the PRECISE option turned on in MOPAC.

Table III. MNDO optimized geometrical data for C2-N1-S-C conformers of [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid obtained from MOPAC 3.1 on a VAX 8800 without and with PRECISE.

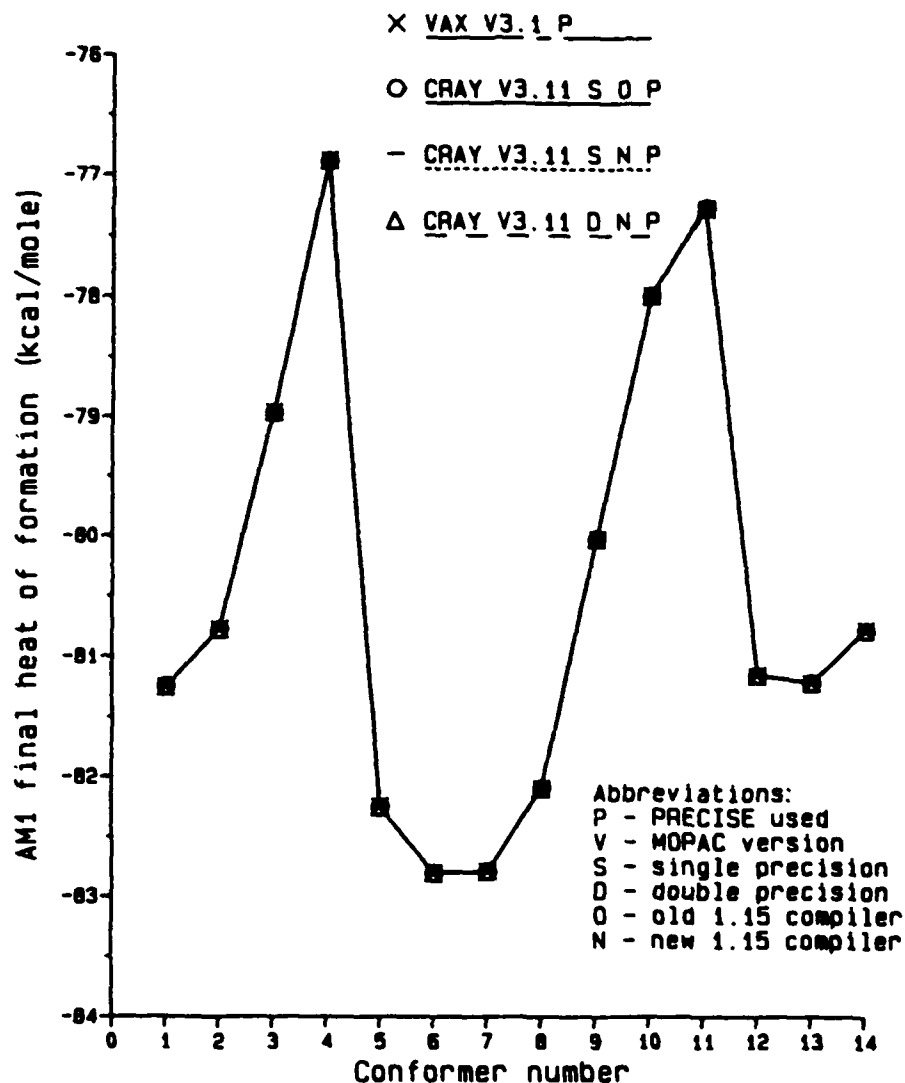| Conformer	C2-N1-S-C (°)	N1-S-C-C (°)		h (Å)	
		without	with	without	with
1	118.5	−64	−66	0.28	0.29
2	140	−64	−65	0.36	0.36
3	170	−6ᴿ	−68	0.43	0.43
4	−160	−83	−89	0.40	0.38
5	−130	−89	−95	−0.27	−0.28
6	−100	−88	−92	−0.15	−0.13
7	−70	−87	−88	−0.03	0.04
8	−40	−85	−79	0.18	0.18
9	−10	−85	−76	0.24	0.25
10	20	−94	−81	0.26	0.25
11	50	−110	−88	0.14	−0.07
12	80	−111	−87	0.07	0.08
13	110	−109	−85	0.25	0.26
14	140	−105	−83	0.37	0.37

Figure 5. AM1 potential energy curves for [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid as predicted by MOPAC on VAX 8800 and Cray X-MP/416 computers. All were computed with the PRECISE option turned on. Curves are labeled as in Figure 2.

Table IV. MINDO/3 optimized geometrical data for C2-N1-S-C conformers of [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid obtained from MOPAC 3.1 on a VAX 8800 without and with PRECISE.

Conformer	C2-N1-S-C (°)	N1-S-C-C (°)		h (Å)	
		without	with	without	with
1	118.5	−65	−68	0.14	0.14
2	140	−67	−79	0.18	0.17
3	170	−88	180	0.14	0.12
4	−160	179	180	−0.09	−0.09
5	−130	179	179	−0.10	−0.10
6	−100	179	178	−0.05	−0.04
7	−70	179	178	0.02	0.02
8	−40	179	180	0.05	0.06
9	−10	180	180	0.04	0.05
10	20	180	180	0.03	0.01
11	50	180	180	−0.01	−0.02
12	80	180	−179	0.02	0.04
13	110	−179	−178	0.12	0.12
14	140	−179	−178	0.17	0.17
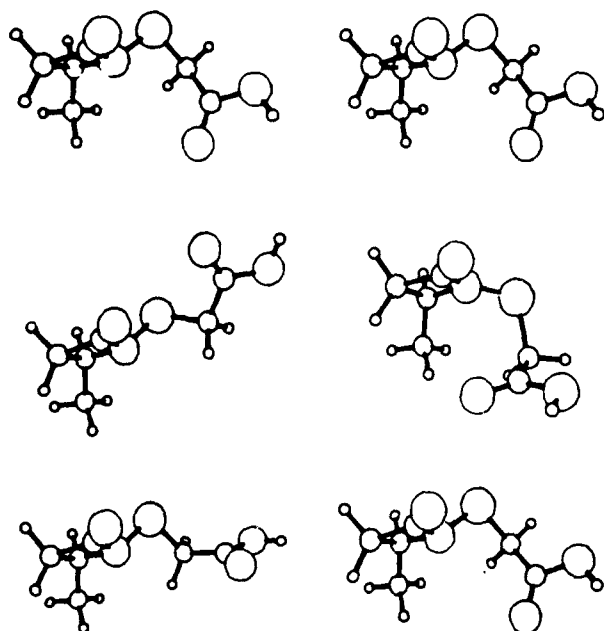
Figure 6. Conformers #2 (top), #12 (middle), and #14 (bottom) from the AM1 calculation done using MOPAC Version 3.1 on the VAX 8800 without (left) and with (right) PRECISE. Conformers #2 and #14 both have a C2-N1-S-C dihedral angle of 140°, and the sulfur and 4α-methyl carbon are on opposite sides of the amide plane. The β-lactam nitrogen has inverted in conformer #12 depending on whether PRECISE is used in the MOPAC reaction coordinate run. The β-lactam carbonyl oxygen projects toward the viewer.

0.14 Å comes closest to the experimental h value of 0.18 Å for a thiamazin with a C2-N1-S-C torsional angle at 119° in the solid state.[29]

The distance h has been associated with antibacterial activity of β-lactam compounds.[36] Following Sweet's crystallographic structure–activity relationship studies, it became commonly believed that compounds with higher h values have better biological activity. Accumulating crystallographic data[37,38] have shown that this concept is not as universally true as once thought.

From the point of a selecting a computational chemistry method that will give reliable h values, the venerable MINDO/3 method is actually superior to the more polished and generally useful MNDO and AM1 methods. Also MINDO/3 predicts the equilibrium β-lactam C—N bond length to be 1.37–1.38 Å (depending on side-chain conformation), which compares favorably with the observed X-ray diffraction value[29] of 1.39 Å. In contrast, AM1 overestimates this length at 1.42–1.44 Å, and MNDO overestimates it even more at 1.43–1.45 Å.

Corresponding to the twofold potentials (Fig. 1–5), the calculated preferred conformations of the model structure are gauche and thus compatible with the crystalline state conformation of a thiamazin.[29] The two low-energy conformers are near −100° and 110°. Indications from temperature-dependent nuclear magnetic resonance (NMR) studies are that sulfenamides in general have barriers to rotation around the N—S bond of 9-23 kcal/mol.[39] Acylation of the nitrogen of a β-lactam would lower this due to delocalization of the nitrogen lone pair. Nevertheless the barrier heights of 4–6 kcal/mol (Fig. 1) that are obtained with the unoptimized AM1 sulfur parameters appear low.[29]

Even though all three of the molecular orbital methods[6-8] were parameterized by Dewar and coworkers on the basis of reproducing experimental heats of formation for a wide variety of molecules, the variety did not include azetidinones. Consequently, it is not surprising that the predicted ΔH_fs for our β-lactam structure vary over a wide range (Fig. 1, 3, and 4). AM1 gives ΔH_fs ca. −80 kcal/mol, MNDO is intermediate at ca. −120 kal/mol, and MINDO/3, which is known to be poor for four-membered rings,[3] gives ca. −180 kcal/mol.

CONCLUSION

The conclusion from these tests is that MOPAC when run with the current default options is not as reliable in terms of reproducibility as many users may have assumed. When certain conformational energy hypersurfaces are being traversed, the molecule can go along different paths on the surface depending on the computer, version, program options, etc. The numerical accuracy of the calculations is having a significant effect on the apparent shape of the surface.

There is no way of estimating how many published calculations of transition state geometries and conformations may have been affected by this hypersensitivity of molecular orbital programs based on the Davidon–Fletcher–Powell[24-27] geometry optimization procedure. Very few papers in the literature reporting MINDO/3, MNDO, and AM1 results have been explicit about whether the calculations were done with the tighter SCF convergence and minimization criteria. We call upon authors to be more specific in the future.

The problem with the minimization procedure uncovered here will not occur for every molecule. It is most likely to occur when the hypersurface traversed is flat. However, it would be difficult to know ahead of time when such a flat surface will be encountered for a complex molecule. Hence the only safe course is to always try out and/or use the tightest available convergence and minimization criteria. As seen in Figure 5, use of PRECISE helps guarantee that the potential energy curves are at least visually similar.

In order to make MOPAC as reliable as possible, a new version with a superior minimization method is under development and will be released after testing.[41] It will also have enhancements stemming from experience of running MOPAC on the Cray. Until the new version is available, calculations with MOPAC, AMPAC, and consanguineous programs should be done with the tightest available convergence and minimization criteria. Such a procedure will cost several times more computer time (see Table I), but such costs are necessary to help insure stable results.

For the test case[40] discussed in this paper, MOPAC ran 13–21 times faster on the Cray X-MP/416 than on a VAX 8800. This increase in speed is encouraging, and even greater increases in speed may be possible if the code were fully customized for the Cray. The speed enhancements achievable with a supercomputer will permit more ambitious computational experiments to be performed even with fine convergence and optimization criteria.

References

1. D. B. Boyd, *Quantum Chem. Prog. Exchange Bull.*, 5, 85 (1985).
2. A. J. Hopfinger, *J. Med. Chem.*, 28, 1133 (1985).
3. T. Clark, *A Handbook of Computational Chemistry: A Practical Guide to Chemical Structure and Energy Calculations*, Wiley-Interscience, New York, 1985.
4. J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 5, 126, 133 (1985), QCPE Program 455, Version 3.0.
5. J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 6, 91 (1986), QCPE Program 455, Version 3.1.
6. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 97, 1285, 1302, 1307 (1975); M. J. S.

Dewar, D. H. Lo, and C. A. Ramsden, *J. Am. Chem. Soc.*, 97, 1311 (1975).
7. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 99, 4899, 4907 (1977).
8. M. J. S. Dewar, E. V. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 107, 3902 (1985).
9. M. J. S. Dewar, *J. Mol. Struct.*, 100, 41 (1983).
10. M. J. S. Dewar, *J. Phys. Chem.*, 89, 2145 (1985).
11. D. F. V. Lewis, *Chem. Rev.*, 86, 1111 (1986). See also, R. E. Christoffersen in *Computer-Assisted Drug Design*, E. C. Olson and R. E. Christoffersen, Eds., American Chemical Society, Washington, DC, 1979, pp. 3–19; D. B. Boyd, *Proc. Natl. Acad. Sci.* (USA), 74, 5239 (1977); K. B. Lipkowitz, R. A. Larter, and D. B. Boyd, *J. Am. Chem. Soc.*, 102, 85 (1980); R. F. Abdulla, D. B. Boyd, N. D. Jones, and J. K. Swartzendruber, *J. Org. Chem.*, 50, 3502 (1985).
12. M. J. S. Dewar, H. Metiu, P. J. Student, A. Brown, R. C. Bingham, D. H. Lo, C. A. Ramsden, H. Kollmar, P. Weiner, and P. K. Bischof, *Quantum Chem. Prog. Exchange Catalog*, 11, 279 (1975).
13. W. J. E. Parr, *Quantum Chem. Prog. Exchange Catalog*, 11, 308 (1975).
14. M. L. Olson and J. F. Chiang, *Quantum Chem. Prog. Exchange Catalog*, 11, 309 (1975).
15. W. Thiel, *Quantum Chem. Prog. Exchange Catalog*, 11, 353 (1978).
16. J. McKelvey, *Quantum Chem. Prog. Exchange Newsletter No.* 69, 16 (1980).
17. M. J. S. Dewar and J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 6, 24 (1986), QCPE Program 506.
18. U. C. Singh and P. Kollman, *Quantum Chem. Prog. Exchange Bull.*, 2, 117 (1982), QCPE Program 446.
19. N. L. Allinger, *J. Am. Chem. Soc.*, 99, 8127 (1977).
20. U. Burkert and N. L. Allinger, *Molecular Mechanics*, American Chemical Society, Washington, DC, 1982.
21. D. B. Boyd, *Drug Inf. J.*, 17, 121 (1983).
22. N. Van Opdenbosh, R. Cramer III, and F. F. Giarrusso, *J. Mol. Graphics*, 3, 110 (1985).
23. SYBYL Molecular Modeling System: VAX-Evans and Sutherland Manual (1985), Tripos Associates, St. Louis, Missouri.
24. R. Fletcher and M. J. D. Powell, *Comput. J.*, 6, 163 (1963).
25. R. Fletcher, *Comput. J.*, 8, 33 (1965).
26. W. C. Davidon, *Comput. J.*, 10, 406 (1968).
27. M. J. D. Powell, *J. Inst. Math. Appl.*, 7, 21 (1971).
28. M. J. Miller, *Acc. Chem. Res.*, 19, 49 (1986).
29. D. B. Boyd, C. Eigenbrot, J. M. Indelicato, M. J. Miller, C. E. Pasini, and S. R. Woulfe, *J. Med. Chem.*, 30, 528 (1987). As reported, the potential energy curves published in this paper were obtained without PRECISE and were smoothed by the interpolation procedure described therein. Consequently the curves are only approximate compared to the curves reported here.
30. D. B. Boyd, in *Frontiers of Antibiotic Research*, H. Umezawa, Ed., Academic Press, Tokyo, 1987, pp. 339–356.
31. M. J. S. Dewar and M. L. McKee, *J. Comput. Chem.*, 4, 84 (1983); M. J. S. Dewar, M. L. McKee, and H. S. Rzepa, *J. Am. Chem. Soc.*, 100, 3607 (1978).
32. K. Steliou, P. Salama, D. Brodeur, and Y. Gareau, *J. Am. Chem. Soc.*, 109, 926 (1987).
33. G. Frenking, *Quantum Chem. Prog. Exchange Bull.*, 7, 76 (1987).
34. J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 6, 99 (1986), QCPE Program 516.
35. C. K. Johnson, ORTEP: A FORTRAN Thermal-Ellipsoid Plot Program for Crystal Structure Illus-

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trations, Oak Ridge Natl. Lab. Report 3794, Oak Ridge, Tennessee, 1965.

36. R. M. Sweet, in *Cephalosporins and Penicillins: Chemistry and Biology*, E. H. Flynn, Ed., Academic Press, New York, 1972, pp. 280–309.

37. D. B. Boyd, in *Chemistry and Biology of β-Lactam Antibiotics*, R. B. Morin and M. Gorman, Eds., Vol. 1, Academic Press, New York, 1982, pp. 437–545.

38. M. Narisada, J. Nishikawa, F. Watanabe, and Y. Terui, *J. Med. Chem.*, 30, 514 (1987).

39. M. Raban and D. Kost, *Tetrahedron*, 40, 3345 (1984).

40. The model structure [[4(S)-methyl-2-oxo-1-azetidinyl]thia]acetic acid or many other MOPAC data sets can serve as formidable tests in future development of not only software related to AM1 and progenitor molecular orbital methods, but also hardware and system software. For instance, during installation of VAX 8800 computers at Lilly in the summer of 1986, extensive checks with MOPAC revealed that the initial releases of the DEC microcode for these machines did not give reproducible results. Identical input data, MOPAC executable images, and hardware gave calculated heats of formation varying erratically beyond the first decimal place. The problem was fixed in subsequent releases of the microcode by DEC. During that same time period, use by a large number of users of assorted other VAX software for molecular mechanics, database management, graphics, word processing, etc., had not detected any problem. Thus MOPAC tested the machines more strenuously than other commonly used software.

41. Note Added in Proof: While this article was in press, one of us (JJPS) readied versions 4.0 and 4.1 of MOPAC and released them through QCPE.[42] As described in the new MOPAC manuals, these versions make use of the Broyden-Fletcher-Goldfarb-Shanno geometry optimizer, which is regarded as superior in its tolerance to round-off errors and can be considerably faster than the Davidon-Fletcher-Powell procedure. For the molecule tested in the present paper,[43] a reduction in VAX 8800 CPU time of 3-8% is obtained with the new optimizer when running AM1. Regarding the shape of the potential energy curves for C2-N1-S-C rotation, it is still necessary to use PRECISE in the new versions. This is true regardless of whether the 1978[31] or 1986[44] MNDO sulfur parameter set is used. Because of the latest improvements in MOPAC, there is little justification for publishing results on highly flexible molecules based upon older versions of the MINDO/3, MNDO, and AMPAC programs without at least rerunning the computations in a modern version of MOPAC as recommended in this article.

42. J. J. P. Stewart, *Quantum Chem. Prog. Exchange Bull.*, 7 (4), supplement 179 (1987); see also, J. Cioslowski and M. Kertesz, *Quantum Chem. Prog. Exchange Bull.*, 7, 159 (1987).

43. A preliminary account of this work, including a listing of the geometrical input data, is given by D. B. Boyd, D. W. Smith, J. J. P. Stewart, and E. Wimmer, in *Science and Engineering on Cray Supercomputers: Proceedings of the Third International Symposium*, J. E. Aldag, Ed., Cray Research, Inc., Minneapolis, Minnesota, 1987, pp. 195–212.

44. M. J. S. Dewar and C. H. Reynolds, *J. Comput. Chem.*, 7, 140 (1986).